

Practitioner's Docket No. MPI95-015P1RCPA1DV1RCEM

U.S.N. 09/801,089

## REMARKS

This Amendment and Response is being filed in reply to the Office Action mailed on January 26, 20005. Applicants thank the Examiner for granting the Request for Continued Examination and for indicating that "integrin-mediated signal transduction" in the context of the application and claims would not be considered indefinite. Applicants have amended claims 21, 22, 41, 43 and 44. No new matter has been added. Claims 21-23, 30 and 32-44 are pending. The rejections in the Office Action are addressed below.

Paragraph 4. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

This paragraph introduces several rejections under this statute. These are addressed separately below.

Paragraph 5. Claims 22-23, 30 and 32-34 were rejected under 35 U.S.C. §112, first paragraph on the grounds that the disclosure does not reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing the application, for reasons set forth in the action mailed March 29, 2004 and maintained in the action mailed August 31, 2004. In particular, this new matter rejection alleges that the generic method comprising the steps of claim 22 and the limitations of claims 23 and 30-34 are not supported by the specification. In the August 31, 2004 action, the Examiner contends that the specification, at pages 37-38 supports two specific methods, but not the generic method of the claims. Applicants respectfully traverse this rejection.

As claim 22 is dependent on claim 21, Applicants include a discussion of claim 21 in this response. Applicants have amended claim 21 from which claim 22 depends (and from which claims 23, 30 and 32-34 depend) to delete the recitation of the ITAM motif and to recite a method to determine whether the cytoplasmic domain of the  $\beta$  integrin subunit is phosphorylated on tyrosine. This generic method of claim 21 is introduced in the specification at page 37, lines 13-15 and more detail of the method adding the tyrosine limitation is provided at, for example, page 37, lines 21-24. The limitation of " $\beta$  subunit" has been deleted from step a) of claim 22, so the steps of claim 22 are the same as the steps of claim 22 as filed (" $\beta$  subunit" was present in 22 c) as filed), except for the previously added limitation of analyzing whether a tyrosine residue is phosphorylated. Applicants believe that a combination of original claim 22 with the disclosure of assaying tyrosine residues from a cell extract on page 37, lines 19-21 provides support for current generic method 22. The specific methods cited by the Examiner in the rejection, i.e. a method for determining metastatic potential (pages 37-38) and a method using GPIIb-IIIa on platelets (Example 1), are examples of this generic method. In Example 1, page 42, line 6. Applicants disclosed that GPIIb-IIIa integrin (having the  $\beta 3$  subunit) was used as the prototype of the invention. So

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using platelets can be considered an example of reducing the generic method to practice. Statements in Examples 4i, 5i, 6i, 7i and 8i provide further specific examples of using the generic method of claim 22. The disclosure of these examples of the generic method comprising the steps of claim 22 show to one skilled in the art that Applicants had possession of the invention at the time of filing the application. In view of this amendment and these remarks, Applicants respectfully request that this rejection be withdrawn.

Paragraph 6. Claims 21-23, 33 and 32-40 were rejected under 35 U.S.C. §112, first paragraph for having new matter in reciting "outside-in or inside-out" signaling. The reasons for this rejection were maintained from the Office action of August 31, 2004. Applicants respectfully traverse this rejection.

Applicants have amended 21 (claims 22-23, 30 and 32-40 dependent thereon) and claim 43 to delete the term "outside-in or inside-out" in regard to the type of signaling. As noted above, the term "integrin-mediated signaling," which remains a limitation in the claims, is not indefinite. Applicants believe that deletion of the term "outside-in or inside-out" obviates this rejection and respectfully request that this rejection be withdrawn.

Paragraph 8. Claims 21-23, 33 and 32-40 were rejected for three separate new reasons under 35 U.S.C. §112, first paragraph, for having new matter. The three new rejections are treated separately below.

A) The Examiner disagreed with the support Applicants found for reciting as a limitation of claim 21 that the  $\beta$  subunit lack an ITAM motif. While additional support for this limitation can be found in an example of the method on pages 42-43, Applicants have deleted this limitation from claim 21 (claims 22-23, 30 and 32-40 dependent thereon), thereby obviating this rejection. In view of this amendment, Applicants respectfully request withdrawal of this rejection.

B) The Examiner stated that original claim 21 does not recite a method of identifying an integrin  $\beta$  subunit, but instead recites identifying the cytoplasmic domain of an integrin. The Examiner further stated that page 37 of the specification discloses identifying phosphorylated tyrosine residues. The Examiner concluded that a method of identifying a phosphorylated  $\beta$  subunit introduces new matter to the claim. As described above, Applicants amended claim 21 to recite the determination of phosphorylation on tyrosine. In traversing the rejection, Applicants point to page 37, lines 13-15, combined with lines 21-24, as discussed above. The elements of claim 21, a) identification of integrin mediated signaling, b) determining phosphorylation of cytoplasmic domain of the  $\beta$  subunit of integrin, and c) determining the phosphorylation of tyrosine residues on the cytoplasmic domain of the  $\beta$  subunit, are all contained in these citations. Therefore, determining the level of tyrosine phosphorylation of the cytoplasmic domain of the  $\beta$  subunit of an integrin is clearly supported by the specification as filed. In view of this amendment and these remarks, Applicants respectfully request that this rejection be withdrawn.

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C) The Examiner found claims 43 and 44 to be generic and gave them the new matter rejection. Applicants have amended claim 43 to limit the method to identify signaling mediated by an integrin wherein it has a  $\beta 3$  subunit. Example 1 provides an example of using this method by making an extract of platelets which express an integrin having a  $\beta 3$  subunit. Other cell types which express an integrin having a  $\beta 3$  subunit could be used in this method, as disclosed in the specification at, for example, page 30, line 21 through page 31, line 11. Applicants believe that this limitation clarifies that these claims were not intended to be generic, except as they relate to an integrin having a  $\beta 3$  subunit. In view of this amendment and these remarks, Applicants respectfully request that this rejection be withdrawn.

The Examiner further requested a dissection of the claims and provision of citations to support each one. The rationale for this request appears to stem from the inclusion of the ITAM limitation in claim 21, and the Examiner's argument that the ITAM limitation is not found in the support for the generic claim. Applicants have deleted the recitation of the ITAM motif from claim 21. The support for amended generic claim 21 can be found in the specification at page 37, as previously described. The support for amended generic claim 22 also was described above. Dependent claim 23 finds support at page 41, line 18, page 43, lines 16-17, and Examples 5i and 6i. Dependent claim 30 finds support at page 43, lines 13-14. Dependent claim 32 finds support at page 38, lines 1-2, page 43, lines 24-25, and Examples 4i, 5i, 6i and 8i. The dependent claim reciting a tumor cell finds support on page 37, line 25 to page 38, line 3. Dependent claim 34 recites the carcinoma species of tumor cell. Examples of this species employed by the methods of the claims can be found in the specification at, for example, in Examples 4i, 5i and 6i. Support for the claims covering the non-elected species similarly can be found in the Examples, as further illustrated on pages 28-32. Applicants believe that they have found support for the limitations of the claims, that the requirements of 35 U.S.C. § 112, first paragraph, are satisfied and that the application as filed showed possession of the claimed invention.

Paragraph 9. Rejection of the Claims Under 35 U.S.C. § 102

Claim 21 was rejected under 35 U.S.C. § 102(b) as being anticipated by Hibbs et al. Hibbs teaches a method to identify integrin mediated signaling comprising determining whether the cytoplasmic domain of an integrin  $\beta$  subunit is phosphorylated. Applicants respectfully traverse this rejection.

Applicants have amended claim 21 to recite a method which determines the phosphorylation of  $\beta$  subunit on a tyrosine residue. Hibbs et al. only detected phosphorylation on serine and threonine (page 1231, Figure 5). Thus, the disclosure of Hibbs et al. does not anticipate the method of amended claim 21. In view of this amendment and these remarks, Applicants respectfully request that this rejection be withdrawn.

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## CONCLUSION

The Amendments and Remarks presented herein are intended to place the present Application in condition for allowance. Applicants respectfully request the timely allowance of the pending claims because, in view of these amendments and remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. § 112 and 35 U.S.C. § 102 are herein overcome. Applicants believe that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned. If the Examiner disapproves of Applicants' amendments and remarks in this Response, Applicants request a prompt mailing of a notice to that effect.

This paper is being filed timely within the three month period for response. No extensions of time are required. In the event any extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

26 April 2005

Respectfully submitted,

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